UNIVERSIDAD NACIONAL AUTÓNOMA DE MÉXICO

FACULTAD DE MEDICINA

DIVISIÓN DE ESTUDIOS DE POSGRADO

Secretaría de Salud de la Ciudad de México

Dirección de Formación, Actualización Médica e Investigación

Curso Universitario de Especialización en Dermatología

"CLAVES PARA MEJORAR LA CALIDAD METODOLÓGICA DE LOS ENSAYOS CLÍNICOS PARA LA PREVENCIÓN DEL CÁNCER QUERATINOCÍTICO EN PACIENTES DE ALTO RIESGO NO INMUNOSPRIMIDOS"

Tesis de Posgrado para obtener el grado de:

Especialista en Dermatología

Presenta:

DRA. MIREYA BARRAGÁN DESSAVRE

Tutor de tesis:
DRA. MARTHA ALEJANDRA MORALES SÁNCHEZ

Ciudad de México a 21 de octubre de 2019

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ABSTRACT

Background: Keratinocyte cancer (KC) is the most common cancer in humans. To our knowledge, no previous publications assessing the methodological quality of clinical trials for the prevention of keratinocyte cancer have been published recently.

Objective: To assess the methodological quality of clinical trials focused on the prevention of KC in high-risk groups not receiving immunosuppressive therapy (NRIT) and propose solutions to improve the design of future trials.

Methods: For this systematic review, we searched clinical trials which main outcome were the prevention of KC in high-risk groups NRIT using the strategy published in PROSPERO registry, CRD42016045981. Two authors made data extraction and article assessments independently and a third author solved discrepancies. CONSORT (Consolidated Standards of Reporting Trials) criteria and Cochrane Collaboration risk of bias tool were used to assess methodological quality.

Results: We analyzed 23 clinical trials. We found a high risk of bias in the following domains: attrition (86.9%) and reporting (60.9%). Regarding CONSORT criteria, in at least 40% of them, authors omitted the following information: description of the trial design, number of losses and exclusions after randomization, results of subgroup and adjusted analysis, estimated effect size and precision of primary and secondary outcomes.

Conclusion: Methodological quality improved in recent published clinical trials compared to those published before the development of CONSORT criteria. All clinical trials should report in detail the information to assess risk of bias.

Key words: keratinocyte cancer, non-melanoma skin cancer, methodological quality, randomized clinical trials, risk of bias.

INTRODUCTION

Keratinocyte cancer (KC), formerly known as non-melanoma skin cancer (NMSC), is the most common cancer in humans and includes basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC). Recently, the standardized incidence rates of the first BCC and cSCC per patient per annum were calculated in 285 and 77 per 100,000 person-years, respectively; in the United Kingdom. The same study reported an increase of 5% in the incidence of KC. **(1)** Although KC rarely cause mortality by itself, morbidity and economic burden from the disease are high; only in the United States, in 2012 the Veterans Health Administration spent $356 million on KC treatment for procedures, prescription drugs and dermatology care. **(2)**

We consider individuals to be at high-risk of development KC if they have a genetic disorder that cause the formation of multiple BCC or cSCC or the diagnosis at an early age; like patients with the following conditions: xeroderma pigmentosum, Gorlin syndrome, Basex syndrome and oculocutaneous albinism. Other high-risk groups are individuals with a previous diagnosed KC and those that developed actinic keratosis (AK), which are considered dysplastic or premalignant skin lesions. Finally, individuals who have received treatments with ionizing radiation and phototherapy are also considered to be at high-risk for KC. **(3)** Immunosuppression is a risk factor for KC and melanoma, and this systematic review excluded clinical trials that recruited participants with HIV infection and transplant recipients, as they are considered to be an immunosuppressed population. **(4)**

Randomized clinical trials (RCT) have been conducted in order to find measures to prevent KC; some have demonstrated to decrease its incidence, while others have shown no benefit in high-risk groups NRIT. However, there is not an updated systematic review for preventing KC in these high-risk groups and in the last Cochrane's review in 2010, it was not possible to perform a meta-analysis of the interventions due to the heterogeneity in reporting the main outcomes. Although the appropriate study design to compare interventions is the RCT, the validity of its results lies in the quality of its execution and the reporting of the results. **(5)** Therefore, the aim of our study was to determine the risk of bias and the quality of publication of the clinical trials focused on the prevention of KC in high-risk groups not receiving immunosuppressive therapy, in order to identify weaknesses and to propose alternatives.

RESEARCH PROBLEM

Most of the clinical trials reported in the articles had a high risk of bias, mainly due to the lack of reporting important methodological aspects.

RESEARCH QUESTION

What is the methodological quality of clinical trials focused on the prevention of keratinocyte cancer in high-risk groups not receiving immunosuppressive therapy?

JUSTIFICATION

The gold standard for ascertaining the efficacy of healthcare interventions, the results obtained in RCT will have an impact on decision making in health care at all levels, from primary care decisions to the formulation of national health policies.

OBJECTIVE

To assess the methodological quality of clinical trials focused on the prevention of KC in high-risk groups not receiving immunosuppressive therapy (NRIT) and propose solutions to improve the design of future trials.

HYPOTHESIS

Does not apply by design.

MATERIAL AND METHODS

We conducted a systematic review focused on the evaluation of the quality of clinical trials focused on the prevention of KC in high-risk groups not receiving immunosuppressive therapy. To identify the clinical trial, we used the search strategy published in the protocol of the Cochrane Systematic Review "Interventions for preventing keratinocyte cancer in high-risk groups not receiving immunosuppressive therapy", published in PROSPERO registry, CRD42016045981. **(6)** Two authors carried out data extraction and a third one review the information. Disagreements were solved by the consensus of the research team. We used the Consolidated Standards of Reported Trials Statement (CONSORT) to assess the quality of the published articles about interventions to prevent KC**. (7)** For the risk of bias assessment, we used the tool described in the Systematic Reviews Manual of the Cochrane Collaboration. **(5)** To avoid redundancy in risk of bias assessment we did not considered the following criteria of the CONSORT statement: 8a, 8b, 9, 10, 11a and 11b.

In order to identify the studies published in the articles we found, we summarized the sociodemographic characteristics and the health condition of the patients, as well as the description of the interventions, their reproducibility, sample size, main outcomes, and adverse events.

RESULTS

We found 22 articles that reported 23 clinical trials focused on the prevention of KC in high-risk groups not receiving immunosuppressive therapy. In these clinical trials, investigators recruited 10,454 participants (2,400 females, 7,859 males and 195 not identified by gender). In all the RCT, male sex predominated (minimum 50%, maximum 100%) and participants had a mean of 60.4 years-old (minimum 3.5, maximum 91 years-old). The largest trial included in this review recruited 2,297 participants **(8),** while the smallest included only 27 participants **(9).** Nineteen studies were multi-centered and four were single-centered. Most of the trials, 78.3% (n=18) were undertaken in the United States of America. (**Table 1**). In twelve studies, the skin phototype was not specified, in the other 11 clinical trials, type II predominated. Inclusion and exclusion criteria were listed in all the trials. Sixteen trials recruited patients with a history of KC **(8-22,24)**, six of them included also patients with AK on the face **(8,9,13,18,19,24).** Two trials included only patients with AK **(23)**. Four RCT recruited patients with the diagnosis of nevoid basal cell carcinoma syndrome, all of them from the same author **(25-28).** One trial included participants with xeroderma pigmentosum syndrome **(29)**. **(Table 1)**

The interventions of the trials were oral nicotinamide **(10, 23),** oral selenium **(11)**, photodynamic therapy (PDT) with 5-aminolevulinate (ALA) **(12, 18**), oral celecoxib **(13,25),** oral beta carotene **(14),** carbon dioxide laser, **(9)** 30% trichloroacetic acid peel **(9),** 5% fluorouracil cream **(9, 24),** low-fat diet **(15),** oral acitretin **(16),** oral retinol **(8, 17),** oral isotretinoin 10 mg **(21),** tretinoin 0.1% crema **(22),** sunscreen

(19), PDT with methyl aminolevulinate (MAL) **(20),** imiquimod 5% cream **(20),** oral vismodegib **(26, 28),** tazarotene 0.1% cream **(27),** T4N5 liposome lotion **(29). (Table 2)**

Regarding follow-up, only three trials assessed their outcomes in a short time, two at four-month and one at an eleven-month period **(23, 13).** The longest period of follow-up was 10.3 years in Clark's clinical trial **(11).** (**Table 2**) To assess reproducibility of intervention, we found all data in the articles except in the clinical trial of Naylor MF et al, which did not specify the amount of sunscreen. **(19)**

In some of the articles, authors failed to describe the process for sequence generation (30.4%), allocation concealment (39.1%) and blinding of the personnel and participants (13%), so they were classified as unclear in risk assessment. High risk of selection bias was found in two articles (8.7%), performance bias in 9 (39.1%), detection bias in 4 (17.4%), attrition bias in 20 (86.9%) and reporting bias in 14 (60.9%). Low risk of selection bias was found in 10 articles (43.5%), performance bias in 11 (47.8%), detection bias in 14 (60.9%), attrition bias in 2 (8.7%) and reporting bias in 6 (26.1%). **Figure 1** shows the frequency of the risk of bias in all of the studies and they were classified by study in the **Table 3**.

From the CONSORT checklist, in at least 40% of them, authors omitted the following information: description of the trial design, number of losses and exclusions after randomization, numbers of participants analyzed, results of subgroup and adjusted analysis, estimated effect size and precision of primary and secondary outcomes, ancillary analyses, registration number and access to the full trial protocol. **(Table 4).** The criteria that the articles meet the least were

the design of the study with 9.09% and presentation of the outcomes in both absolute (risk ratio, relative risk or odd ratio) and relative (risk difference) effect sizes. Most papers did not specify if the trial was parallel, sequential, cross-over, factorial or cluster.

DISCUSSION

Most of the clinical trials reported in the articles had a high risk of bias, mainly due to the lack of reporting important methodological aspects. This lack of information is common in clinical trials focused on dermatology conditions as stated by the review of Sanclemente G. **(30)**

According to our results, the high risk of selection bias is due to the lack of information about the process to generate the random sequence (4.35%) and the allocation concealment (8.7%). Even though the randomization is carried out correctly, the possibility of knowing or suspecting the future assignments may arise selective recruitment of participants. To prevent the risk of selection, allocation sequence and concealment allocation should be properly performed and described, because these activities are always possible. The results of several methodological investigations, found that, for subjective outcomes, trials that used inadequate or unclear allocation concealment yielded 31% larger estimates of effect than those that used adequate concealment, while trials that were not blinded yielded 25% larger estimates**. (7)**

The high risk of detection bias was not common, only in 17.4% of the studies the personnel who assessed the main outcome were not blinded. Of the 23 clinical trials we analyzed, blinding was not viable in four. In the first one, patients were randomized into two groups, one received PDT and the other one was only observed. **(12)** In the clinical trial conducted by Hantash BM et al **(9)** interventions were completely different among intervention groups (carbon dioxide laser vs. 30% trichloroacetic acid peel vs. 5-fluorouracil cream). In the article of Jaax S et

al **(15)** one group had a diet established by a nutritionist while the other group continued with their usual diet. Sotiriou E et al **(20)** ran an intraindividual comparison study, where PDT with MAL cream was applied to the same patient in the middle of the face and imiquimod 5% cream in the other half.

In our study, 39.13% of the RCTs had high risk of performance bias because authors did not describe how participants and outcome assessors were blinded to interventions. Despite guidelines recommend to describe the blinding process, the frequency of explicit reporting of the blinding status of study participants and personal remains low even in trials published in top journals. **(5)** Besides all the efforts of the research team to blind outcome assessors (investigators and participants) some interventions like laser-assisted procedures, photodynamic therapy and diet are difficult to blind because they differ in the application technique, administration route, treatment duration and the adverse effects.

The attrition bias was high risk in 86.96% of the clinical trials analyzed due to the longtime of follow-up, months to years. Evidently, the bias is higher when the dropouts are different in magnitude between groups and with different causes or if they are related to the intervention. To asses this bias, some studies such as Elmets CA et al **(13)** compared the basal characteristics of the dropout group with the group of patients that completed the study, in order to determine if there were differences that could explain the uncompleted follow up. About the dropouts in a trial, CONSORT facilitates the evaluation of this point with a flowchart, which has become mandatory in every intervention study; and only 27.27% of the articles

failed to include this flowchart. All of them were articles published before the recommendations of CONSORT statement.

We found a very high risk of reporting bias (60.9%) in our study because there is a lack of congruence between the outcome variables set a priori in the protocol and the ones reported in the published article. We identified that authors tend to report the results of outcomes that differ among intervention groups and have statistical significance. Regarding the reporting bias, some trials had to be suspended before the established time for different reasons: 1) decision of the investigators and the ethics committee **(12),** 2) Food and Drug Administration (FDA) found an association between COX-2 inhibitors and cardiovascular adverse events **(13),** 3) lack of financial funds **(8),** and 4) experimental intervention was statistically more effective than placebo. **(26)** According to the CONSORT, most clinical trials did not report the results of all the outcomes that were initially established, a practice that in most cases leads to the overestimation of efficacy and the underestimation of safety risks of interventions. **(31)**

On the other hand, none of the studies fulfilled all of the items of CONSORT checklist, not even the most recent ones. Recently, Kim DY et al showed that the overall reporting quality of RCTs in the dermatology literature has improved compared with that in the past. **(32)** In 2006, the proportion of trials describing randomization methods was 45% among RCTs published in JAAD and BJD, whereas their results showed that 70% of recently published RCTs described randomization methods. In our study, we found that those RCT published before XXI century did not explained all the methodology aspects, so it was difficult to

accomplish with CONSORT criteria. To improve the RCT report some dermatology journals like the Journal of the American Academy of Dermatology (JAAD), Journal of the American Medical Association (JAMA), the Journal of Investigative Dermatology (JID) and the British Journal of Dermatology (BJD); have endorsed the CONSORT statement on the basis of the journals' instructions for authors.

Analyzing the results of our review, we conclude that the evidence of efficacy and safety of some interventions is compromised due to the high risk of bias in some domains, mainly performance, attrition and reporting bias. We recommend investigators to describe in detail all the information necessary to assess those risks of bias. Although this review identified RCTs for secondary prevention of KC in high risk groups, few trials assessed interventions in participants with genodermatoses such as albinism or xeroderma pigmentosum (XP); most of them included participants with KC history or AK. For rare diseases like XP or albinism, we suggest designing multi-centered RCT, in order to recruit large samples of participants that meet the inclusion criteria.

Finally, in some trials, we did not find the declaration of conflict of interest of authors and the source of funding. The lack of information about the involvement of pharma industry in RCT could suggest an industry bias that could explained favorable efficacy results in studies sponsored by these companies compared with RCT sponsored by universities, as stated by Lundth et al. **(33)** However, in our review most of the RCT were funded by research grants and universities' funds. In fact, almost all the industry-sponsored RCT fulfilled the CONSORT's

criteria and authors explained in detail all the procedures we needed to assess the risk of bias, so we considered low the risk of overestimating the interventions' effects.

The limitations of our study relied in the lack of information to assess the risk of bias in articles published in the 90's, mainly in the reporting bias, because we did not find the protocols in the databases of clinical trials, neither ClinicalTrials.gov nor European Union Clinical Trials Registry. Although most of trials assessed the efficacy of intervention with the same primary outcome, authors used different forms of measure, for example, to report incidence of new KC, some authors reported the number of KC per group of intervention while other reported the number of participants with a new KC per group. Despite these differences did not affect the quality of the evidence, this lack of consensus makes difficult to do a quantitative synthesis of the results of the interventions, a meta-analysis.

CONCLUSIONS

As RCTs are the gold standard for ascertaining the efficacy of healthcare interventions, the results obtained in RCT will have an impact on decision making in health care at all levels, from primary care decisions to the formulation of national health policies. **(7)** Therefore, we encourage research teams focused in skin cancer prevention to join efforts to design and report RCT according to CONSORT criteria and with all the information to assess risk of bias. Over time, the quality of clinical trials has been improved because journals, every day more, demand compliance to the CONSORT statement. However, it is important that all the journals request for the fulfillment of these criteria in order for articles to be accepted.

RECOMENDATIONS

Regarding outcomes, to assess secondary prevention of KC we strongly recommend that the main outcome of the RCT should be the number of participants who developed a new KC, additional to the total number of new tumors per group of intervention. Investigators should also specify the number of basal cell carcinomas and squamous cell carcinomas independently, in order to assess the benefit per type of KC. All the trials reported the adverse events serious enough to lead to withdrawal and we suggest including the number of adverse events per group. As secondary outcomes of efficacy, RCTs should report recurrence, time to recurrence (defined as the time between the start of the intervention and the return of the KC at the same site of the body), second or subsequent KC, mortality related to KC, changes in quality of life and markers of sun damage. It would also be ideal to report the total number of AK and the proportion of participants with complete clearance of AK after interventions. Finally, due to the long latency period to develop a subsequent KC, a follow-up of at least 5 years should be carried out in all RCT for detecting the main outcome and recurrences.

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SUPPLEMENT

Table 1. General characteristics of patients participating in the 17 clinical trial included on the review

	Author / year / country	Clinical status of patients	Age prom ± SD med (p25-p75)~ (min-max)~~	Male gender n (%)	Predominant phototype (Fitzpatrick skin type)	Predominant topography
1	Chen AC / 2015 / Australia	≥ 2 histologically confirmed KC in the previous 5 years	66.4 ± 11.8 (30-91)	243 (63%)	NI	NI
2	Clark LC / 1996 / USA	History of ≥ 2 BCCs or 1 SCC with 1 of these carcinomas occurring within the prior year	63.2 ± 10.1 (18-80)	980 (74.7%)	II	NI
3	Dixon A / 2014 / Australia	≥ 1 histologically proven invasive KC	71	36 (57%)	NI	Face
4	Elmets CA / 2010 / USA	10–40 AK and a previous histological diagnosis of ≥ 1 AK and/or KC	65.2 ± 10.2 (37.5-87.6)	197 (82%)	II	Upper extremities, neck, face, and scalp
5	Greenberg ER / 1990 / USA	History of ≥ 1 biopsy proved of BCC or SCC	63	1,251 (69.3%)	III	NI
6	Hantash BM / 2006 / USA	History of KC and numerous AKs or significant photodamage alone	72.8 (54-91)	27 (100%)	Does not specify predominance I, II, y III	Face and scalp
7	Jaax S / 1997 / USA	KCs who had no > 2 previous KCs	51.45 ± 11.45	70 (60.8%)	NI	NI
8	Kadakia K / 2012 / USA	History of ≥2 KCs confirmed HP	68.2 ± 9.48	44 (62.8%)	II	NI
9	Levine N / 1997 / USA	History of ≥ 4 BCCs and/or SCCs, the most recent diagnosed in the previous year	NI	379 (72.2%)	I-II	NI
10	Marcus S / 2017 / USA	Facial AKs, history of KCs, and histologic evidence of dysplasia	NI	NI	NI	NI

		within clinically normal-appearing perilesional skin				
11	Moon TE / 1997 / USA	History of > 10 AKs, the most recent diagnosed during the preceding year and ≥2 pathologically confirmed SCC or BCC	63	1,618 (70%)	I-II	NI
12	Naylor M / 1995 / USA	Clinical evidence of AKs or KCs	63.75 ± 8	86%	II	NI
13	Sotiriou E / 2015 / Greece	Field cancerization + history of ≥ 1 previous KCs	65 ± 6.8	37 (84)	III	Scalp
14	Surjana D / 2012 / Australia	≥ 4 palpable AKs	**Study 1:** 72 (52-90) **Study 2:** 70 (48-89)	NI	NI	Face, scalp and upper limbs
15	Tang JY / 2010 / USA	BCNS + ≥ 4 histologically verified BCCs during the year before	45 ± 12	32 (53%)	NI	NI
16	Tang JY / 2012 / USA	BCNS with ≥ 10 surgically eligible BCCs or removed during the previous 2 years	53.5 ± 8	27 (65.8%)	NI	NI
17	Tang J / 2014 / USA	BCNS	52 ± 10	17 (50%)	NI	Back
18	Tang J / 2016 / USA	BCNS with ≥ 10 surgically eligible BCCs	54 ± 8.25	66%	NI	NI
19	Tangrea JA / 1992 / USA	≥ 2 biopsy-proven BCCs during the 5 years	60.8	736 (77.3%)	II	NI
20	Weinstock M / 2012 / USA	≥ 2 KCs in the prior 5 years but free of KC at enrollment	NI	1097 (96.9%)	NI	Face and ears
21	Weinstock MA / 2018 / USA	History of ≥ 2 KCs in the past 5 years	71.1 ± 9.3	916 (98%)	III	Face and ears
22	Yarosh D / 2001 / USA	Xeroderma pigmentosum + history of AK or KC	17.75 (3.5-53)	8 (27.5%)	I – II/III	Face and arms

AK: actinic keratosis. **BCC:** basal cell carcinoma. **BCNS:** basal cell nevus syndrome **KC:** Keratinocyte cancer. **NI:** no information. **SCC:** squamous cell carcinoma.

Table 2. Sample size, follow-up time and comparison of the interventions of the studies included in the review.

	Author / year	Sample size	Intervention	R	Comparison	R	Follow-up after randomization
1	Chen AC / 2015	386	Oral nicotinamide 500 mg bid for 12 months	Yes	Placebo	Yes	18 months
2	Clark LC / 1996	1,312	Oral selenium 200 mcg qd for mean 4.5 years (2.8)	Yes	Placebo	Yes	6.4 (0-10.3) years
3	Dixon A / 2014	63	Two ALA-PDT 14 days apart + AHA 10% bid 2 weeks before PDT	Yes	Observation	Yes	34 (13-38) months
4	Elmets CA / 2010	240	Oral celecoxib 200 mg bid for 9 months	Yes	Placebo	Yes	11 months
5	Greenberg ER / 1990	1,805	Oral beta carotene 50 mg qd	Yes	Placebo	Yes	5 years
6	Hantash BM / 2006	27	Carbon dioxide laser resurfacing or 30% trichloroacetic acid peel	Yes	5% fluorouracil cream bid for 3 weeks	Yes	2 years
7	Jaax S / 1997	115	Diet with 20% of calories from fat for 2 years	Yes	Usual diet	Yes	2 years
8	Kadakia K / 2012	70	Oral acitretin 25 mg 5 days/week for 2 years	Yes	Placebo	Yes	2 years
9	Levine N / 1997	525	Oral retinol 25,000 UI or oral isotretinoin 5-10 mg qd for 3 years	Yes	Placebo	Yes	3 years
10	Marcus S / 2017	166	Two ALA-PDT treatments or three ALA-PDT treatments	No	Vehicle-PDT	No	1 year
11	Moon TE / 1997	2,297	Oral retinol 25,000 UI qd for 5 years	Yes	Placebo	Yes	5 years
12	Naylor M / 1995	53	29 sun protection factor sunscreen for 2 years	No	Placebo	No	2 years
13	Sotiriou E / 2015	50	MAL cream 160 mg/g + PDT (Two treatment sessions 1 week apart)	Yes	Imiquimod 5% cream 250 mg 3 non-consecutive days of the week (Two 4-week courses with 2-week treatment-free between them)	Yes	1 year

14a	Surjana D / 2012	35	Oral nicotinamide 500 mg bid for 4 months	Yes	Placebo	Yes	4 months
14b	Surjana D / 2012	41	Oral nicotinamide 500 mg qd for 4 months	Yes	Placebo	Yes	4 months
15	Tang JY / 2010	60	Oral celecoxib 200 mg bid for 3 years	Yes	Placebo	Yes	3 years
16	Tang JY / 2012	41	Oral vismodegib 150 mg for 18 months	Yes	Placebo	Yes	8 (1-15) months
17	Tang J / 2014	34	Placebo for 12 months + tazarotene 0.1% cream qd for 24 months	Yes	Tazarotene 0.1% cream qd for 12 months + placebo for 24 months	Yes	3 years
18	Tang J / 2016	41	Oral vismodegib 150 mg/day for 18 months	Yes	Placebo	Yes	3 years (median)
19	Tangrea JA / 1992	981	Oral isotretinoin 10 mg qd for 3 years	Yes	Placebo	Si	3 years
20	Weinstock M / 2012	1,131	Tretinoin 0.1% cream bid for 5.5 years	Yes	Placebo	Yes	3.47 years (mean)
21	Weinstock MA / 2018	932	Fluorouracil 5% cream bid for 2-4 weeks	Yes	Placebo	Si	2.7 years (mean)
22	Yarosh D / 2001	30	T4N5 liposome lotion for 1 year	Yes	Placebo	Yes	18 months

ALA: aminolevulinic acid. **bid:** 2 times/day. **MAL:** methyl aminolevulinate. **PDT:** Photodynamic therapy. **qd:** 1 time/day. **R:** reproducible.

Table 3. Risk of bias according to the tool of the Cochrane Collaboration

	Author /year	Selection bias (randomization)		Performance bias	Detection bias	Attrition bias	Reporting bias
		Sequence generation	Allocation concealment				
1	Chen AC / 2015	Low risk	Low risk	Low risk	Low risk	High risk	High risk
2	Clark LC / 1996	Unclear risk	Low risk	Low risk	Low risk	High risk	Unclear risk
3	Dixon A / 2014	Low risk	Low risk	High risk	Unclear risk	High risk	High risk
4	Elmets CA / 2010	Low risk	Unclear risk	Unclear risk	Low risk	High risk	High risk
5	Greenberg RA / 1990	Low risk	Low risk	Low risk	Low risk	High risk	Low risk
6	Hantash BM / 2006	High risk	High risk	High risk	High risk	High risk	Unclear risk
7	Jaax S / 1997	Low risk	Unclear risk	High risk	Low risk	High risk	High risk
8	Kadakia K / 2012	Unclear risk	Unclear risk	High risk	High risk	High risk	High risk
9	Levine N / 1997	Low risk	Unclear risk	Low risk	Low risk	High risk	High risk
10	Marcus S / 2017	Unclear risk	Unclear risk	Low risk	Unclear risk	High risk	High risk
11	Moon T / 1997	Low risk	Low risk	High risk	Low risk	High risk	High risk
12	Naylor M / 1995	Unclear risk	Unclear risk	Low risk	Unclear risk	High risk	High risk
13	Sotiriou E / 2015	Low risk	High risk	High risk	High risk	Low risk	High risk
14	Surjana D / 2012 A	Low risk	Low risk	Low risk	Low risk	High risk	High risk
15	Surjana D / 2012 B	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
16	Tang JY / 2010	Unclear risk	Unclear risk	Unclear risk	Unclear risk	High risk	High risk
17	Tang JY / 2012	Low risk	Low risk	Low risk	Low risk	High risk	High risk
18	Tang J / 2014	Unclear risk	Unclear risk	Unclear risk	Unclear risk	High risk	High risk
19	Tang J / 2016	Low risk	Unclear risk	High risk	Low risk	High risk	Low risk

20	Tangrea JA / 1992	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
21	Weinstock M / 2012	Low risk	Low risk	High risk	High risk	High risk	Low risk
22	Weinstock MA / 2018	Low risk	Low risk	High risk	Low risk	High risk	Low risk
23	Yarosh D / 2001	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Total		High 1 (4.35%) Low 15 (65.22%) Unclear 7 (30.43%)	High 2 (8.7%) Low 12 (52.17%) Unclear 9 (39.13%)	High 9 (39.13%) Low 11 (47.83%) Unclear 3 (13.04%)	High 4 (17.4%) Low 14 (60.87%) Unclear 5 (21.74%)	High 20 (86.96%) Low 2 (8.7%) Unclear 1 (4.35%)	High 14 (60.9%) Low 6 (26.09%) Unclear 3 (13.04%)

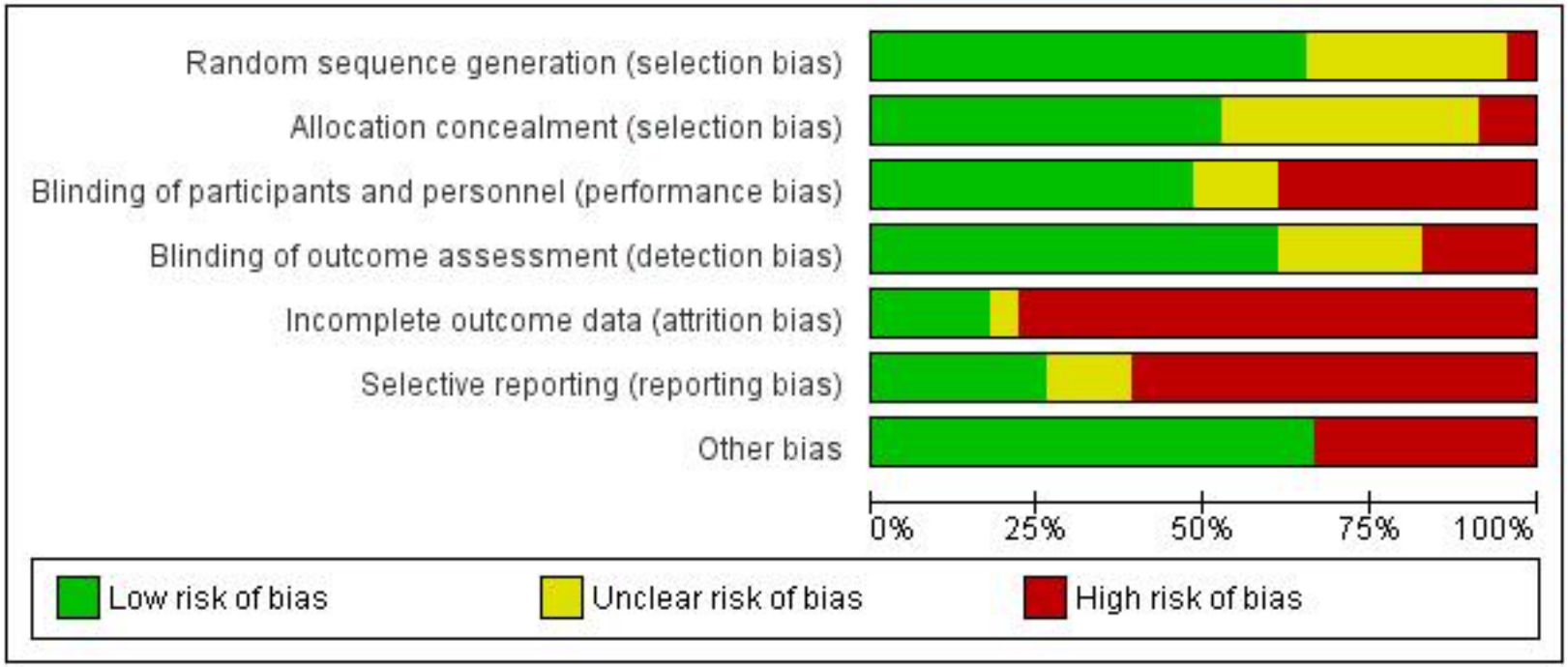

Figure 1. Frequency of risk of bias in the clinical trials for KC prevention

Table 4. Summary of the quality of clinical trial reports included based on CONSORT criteria

CONSORT Checklist	Total of clinical trials reviewed 23 (100%)
Identification as a randomized trial in the title	15 (68.18%)
Abstract	12 / 21 (57.1%) *
Scientific background	17 (77.27%)
Specific objectives or hypotheses	22 (100%)
Description of trial design	2 (9.09%)
Important changes to methods after trial commencement with reasons	7 (31.82%)
Eligibility criteria for participants	21 (95.45%)
Settings and locations where the data were collected	13 (59.09%)
The interventions for each group with sufficient details to allow replication	20 (90.91%)
Completely defined pre-specified primary and secondary outcome measures	19 (86.36%)
Any changes to trial outcomes after the trial commenced, with reasons	2 (9.09%)
How sample size was determined	12 (54.55%)
When applicable, explanation of any interim analyses and stopping guidelines	6 (27.27%)
Statistical methods used to compare groups for primary and secondary outcomes	21 (95.45%)
Methods for additional analyses	19 (86.36%)
For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome.	16 (72.73%)
For each group, losses and exclusions after randomization, together with reasons	13 (59.09%)
Dates defining the periods of recruitment and follow-up	20 (90.91%)
Why the trial ended or was stopped	11 (50%)
A table showing baseline demographic and clinical characteristics for each group	20 (90.91%)

For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	8 (36.36%)
For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	3 (13.64%)
For binary outcomes, presentation of both absolute and relative effect sizes is recommended	6 (27.27%)
Results of any other analyses performed, including subgroup analyses and adjusted analyses	9 (40.91%)
All important harms or unintended effects in each group	19 (86.36%)
Trial limitations	16 (72.73%)
Generalisability (external validity, applicability) of the trial findings	19 (86.36%)
Interpretation	20 (90.91%)
Registration number and name of trial registry	12 (54.55%)
Where the full trial protocol can be accessed, if available	15 (68.18%)
Sources of funding and other support (such as supply of drugs), role of funders	21 (95.45%)

* 21 RCTs were evaluated because two studies were sent as a letter to the editor